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A RE-EVALUATION OF NUTRITIONAL GOALS – NOT JUST DEFICIENCY COUNTS

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ABSTRACT

There is considerable controversy about the soundness and relevance of so-called "megavitamin" therapy for various illnesses. In this article it is suggested that this disagreement is caused to a large extent by the use of two very different approaches to nutrition, which are referred to here as the "nutritional need" and "optimal intake" approaches. It is clear that a re-evaluation of the goals of nutrition is required, as nutritional recommendations deal mainly with the prevention of deficiency diseases and are not concerned with optimal levels of intake.

THE NUTRITIONAL NEED APPROACH

Originally some deficiency diseases, such as pellagra and beri-beri, were thought to be infections. Typically, classical infectious diseases are all-or-none diseases: either a person has pneumonia or they do not. Deficiency diseases were thought to be of a similar nature, i.e. it seemed as if a person was either affected by a deficiency or they were not. Although the cause of deficiency was subsequently found to be different, the all-or-none conception still remained. In this all-or-none description of deficiency, "nutritional need" is the critical daily intake which divides the two states of health: sick and well. Thus nutritional need corresponds to the smallest amount which prevents deficiency. This conceptual framework leads to the attitude that, when there is no obvious deficiency, no benefit can be derived from increased amounts of essential nutrients.

The all-or-none notion of deficiency is widely accepted, at least implicitly. For example, it is assumed in Recommended Dietary Allowances (RDA)(1). In these recommendations nutritional need is used as a basic concept, yet no attempt is made to examine its full implications. The assumption of the all-or-none nature of deficiency is, however, an oversimplification of the effects of nutrients on the body. A severe deficiency is only a pre-morbid condition with an

extremely low concentration of a nutrient in the body. The rates of typical biochemical reactions of nutrients change smoothly with concentration and thus the idea of an exactly quantifiable "nutritional need" seems to be unintelligible at the biochemical level, because it implies that sudden changes would occur between deficiency and normal health (2, 3). "Nutritional need", "physiological requirement", and "adequate amount" may be acceptable in everyday language, but they should not be allowed to distract attention from the smooth dose-effect relationship between nutrient intake and the body's metabolic processes.

In an attempt to alleviate the crudeness of the all-or-none approach, the terms "marginal" and "subclinical deficiency" have sometimes been used to denote the region between a severe deficiency and normal health. This division of health into three states is also arbitrary, even if it may be practical in some cases.

THE OPTIMAL INTAKE APPROACH

Instead of being satisfied with the absence of overt signs of deficiency it is possible to aim for optimal levels of intake. The "optimal intake" approach seems to have a valid biochemical basis (2). A gradual increase in nutrient concentration in the body from a very low to a very high level results in a change from deficiency to toxicity. Accordingly, deficiency and toxicity are respectively caused by too-low and too-high rates of reaction. The reactions associated with the physiological signs of deficiency and of toxicity are usually different. Somewhere between these extremes are optimal concentrations and reaction rates, which promote the best possible metabolic functioning of the body, i.e. "best possible" health with respect to the nutrient in question. These optimal concentrations are maintained by optimal levels of intake.

"Health" is a concept which only has relevance at the physiological level, and thus optimal levels of intake cannot be derived solely from biochemical data. However, biochemical knowledge may suggest which physiological processes intake levels may affect most. Moreover, health is a vague and non-quantifiable expression, but it can be given operational interpretations such as morbidity and mortality at population level. At an individual level, controlled tests or the "trial and error" method allow comparison of the effects of different amounts of nutrients over a short period.

Differences between people at the biochemical level may be expected to cause large variations in individuals' optimal levels of intake. Such individuality with respect to nutrition has been illustrated by experiments with laboratory animals (4, 5). Furthermore, within an individual, the optimum level may be affected by various factors, such as diseases, which cause changes in the body at the biochemical level. Thus a specific optimum level which is the same for all people, or even constant for an individual, cannot be expected. Also, the top of the "health condition against nutrient intake" curve may well be quite a wide plateau and is most unlikely to have a sharp peak corresponding to an exact level of intake. Thus, in practice, the

optimal intake approach is no easier than the mere prevention of deficiencies, yet it appears to be biochemically valid, in contrast to the nutritional need approach.

Originally the optimal intake approach was proposed as a method of psychiatric treatment, with its main goal the "optimum concentrations of substances normally present in the body" (6). This was labeled the "orthomolecular" approach.

It has been pointed out that an exact "ideal intake" or "ideal diet" is unattainable (7). This is true, for example, because of biological variations. However, in many fields of science exact values and solutions are not attainable, but approximations are made and approximate values aimed for. In the same way, approximation of optimal amounts at a population and at an individual level would seem a sound goal in the field of nutrition.

Sometimes the optimal intake (i.e. orthomolecular) approach is misunderstood to assume that a larger intake always leads to better health. The fact that very large amounts of particular nutrients are found to be toxic in some cases is used as a counter-argument to such an approach (8, 9). In fact the optimal intake approach, by definition, aims at optimal amounts for health. Toxic amounts, by definition, exceed optimal levels, and any possible nutrient supplementation should obviously stay below these levels. Actually, many essential nutrients are virtually non-toxic in quantities much higher than the RDA level (1, 10).

There is nothing particularly ingenious about the optimal intake approach, except that it is in strong discord with the approach used in RDA and with the traditional approach in general. RDA levels are not optimal and they are not intended to be. Indeed, in RDA it is not taken into account that the reaction rates and metabolic processes of the body depend on concentrations and thus on levels of intake (1, 2).

VITAMIN C - GENERAL OBSERVATIONS

Vitamin C is an interesting example of a nutrient, as man is among the very rare mammalian species unable to synthesize it (11), and because it has been a subject of intense controversy amongst those interested in nutrition.

Biochemical data do not provide a basis for evaluating optimal intake levels for vitamin C; but concentration and reaction rate changes, seen at the biochemical level, suggest that physiological effects may be expected, either beneficial or harmful. If a large intake does not affect the levels in the body e.g. because of effective saturation of intestinal absorption, then these large intake levels may be expected not to have any effect on the metabolic functions of the body, except perhaps within the intestines and stomach. Even the latter possibility is sometimes worth considering. For example, it has been suggested that vitamin C may prevent the formation of carcinogenic nitrosamines by reacting with nitrite within the stomach (12, 13).

It is sometimes argued that large doses of vitamin C have no physiological effect, because "surplus" is excreted in urine. However, increasing a single ingested vitamin C dose from 1.5 to 12 grams causes a monotonous increase in the peak concentration in blood plasma (4). The plasma concentration in the body is of principal physiological importance as it affects metabolic processes, while the excretion rate of unmetabolized vitamin C is of minimal physiological interest. Moreover, as the vitamin C dose is increased from 1.5 to 12 grams there is a decrease in the percentage of the vitamin that is absorbed from 50 % to 16 % yet the absolute amount absorbed is increased from 0.7 to 1.9 grams (14). Thus, in this case, there is no simple saturation of intestinal absorption. Instead, a higher intake causes more vitamin C to be absorbed causing a higher level in the body. However, in the long term vitamin C metabolism is altered by regular ingestion of large doses thereby complicating the dose-concentration relationship (15).

Clear signs of scurvy appear when the vitamin C concentration in the plasma decreases below 0.2 mg/dl (16), while high intakes may increase vitamin C concentration up to 2-3 mg/dl (14, 17). Accordingly, large variations in the rates of some ascorbate-dependent reactions may be expected; but, as noted above, the higher levels may or may not be beneficial. Data at the physiological level is needed to determine which amounts are best for health.

VITAMIN C - NUTRITIONAL ASPECTS

The evaluation of experimental data depends upon a conceptual framework. The nutritional need and optimal intake approaches correspond to two different "paradigms", to use Kuhn's terminology (18). The "paradigm" is the network of basic assumptions, concepts and values in a scientific field. Accordingly, the paradigm determines what may be considered worth studying, what may be taken as an axiom or as an illusion, what are reasonable criteria for "proof" etc. Differences in the paradigms used in the two approaches may be seen from the arguments put forward in discussion of, for example, the effect of vitamin C on the common cold.

If the sole function of vitamin C is taken to be the prevention of scurvy, then there is no accounting for the fact that in many studies vitamin C, taken in amounts well above the RDA level, has been found to alleviate the symptoms of the common cold. Accordingly, the nutritional need paradigm causes this phenomenon to be artificially labeled "pharmacological" as it does not relate to scurvy, and the conclusion to be drawn that the effect is so small that vitamin C can not be suggested as a "drug cure" for the common cold (1, 19, 20).

On the other hand, if optimum dosage is the goal, then the several studies which have found that large amounts of vitamin C do ameliorate common cold symptoms suggest that the optimum dose for vitamin C is well above the RDA level (21). The studies which have not found a beneficial effect of vitamin C on cases of the common cold have not found toxic effects either, and thus do not suggest that the amounts used were significantly in excess of the optimum range. Moreover,

inconsistencies in the results of common cold studies may largely result from uncontrolled variables such as the basal vitamin C intake. As an extreme example, in one study the control group excreted on average ca. 300 mg of vitamin C in urine per day (22), and the intake level must have been even higher. Instead, the relevant question should be whether a low level of intake, say, 60 mg/day (RDA level) results in longer lasting and more severe symptoms of the common cold than higher amounts which may be expected to be nearer to the optimal level. Thus very different conclusions can be drawn from the same set of data by using different paradigms.

There is limited data available about the effect of vitamin C intake level on population health, but in one study with people over 50 years old it was found that a vitamin C intake of less than 50 mg/day was accompanied by over twice the mortality rate during the seven years of study as compared with a group with a higher intake level (23). In another study, general state of health was determined by the Cornell Medical Index Health questionnaire. The group which had a vitamin C intake of over 200 mg/day had on average 18 % fewer clinical symptoms and signs than the group with an intake of less than 100 mg/day. The group with an intake of 100-200 mg/day was also between the other groups in its average number of symptoms and signs (24). Furthermore, a negative correlation between vitamin C intake and standard mortality ratios for several diseases in different regions of the United Kingdom has been found (25). In the nutritional need framework such findings may seem arbitrary as they are not related to clear signs of scurvy; but, when taking into account the actual changes at the biochemical level due to a higher intake of vitamin C, these data suggest that a higher intake is closer to the optimum within the region studied.

In contrast to this, the RDA level for vitamin C is 60 mg/day. It has been chosen only because it provides "adequate reserves" for about one month before the development of obvious signs of scurvy. It is not chosen because any beneficial effects are to be expected from taking just 60 mg/day (1, 2).

Vitamin C also serves as an example of how external factors may affect the optimum level. In rats, which are able to synthesize vitamin C internally, certain foreign compounds dramatically increase vitamin C production (26). This suggests that a higher concentration in the body may be closer to the optimum in such a case. In fact, vitamin C is known to participate in drug metabolism (27). An example of metabolic differences between population groups is that of tobacco smokers, who have a lower level of vitamin C in the blood than non-smokers with the same level of intake (28). Thus the optimal intake level must be higher in smokers if the same level in blood corresponds to optimum. Moreover, it is even probable that the level in blood corresponding to optimum is higher for smokers due to a need for a higher rate of metabolism of foreign compounds. This implies an even higher optimum intake level for smokers.

There are many interesting reports which claim the efficacy of high doses of vitamin C in treating a variety of medical disorders (21, 29-43). Such claims cannot be discounted on biochemical grounds. Yet more

studies are needed to evaluate optimum levels of vitamin C, for prevention of illness in healthy people and for treatment of the sick.

THE ROLE OF NUTRIENTS IN ENZYME FUNCTION

Many vitamins and trace elements serve as co-factors of enzymes. Binding of co-factors to enzymes is a true saturation process, as only the bound fraction may be expected to serve the co-factor function. The degree of saturation depends on the co-factor concentration but maximum saturation is approached only slowly as the concentration is increased.

For enzymes it is functionally valid to assume that maximal saturation would be better than any intermediate degree of saturation. Higher enzyme activity would allow a higher metabolic flux when necessary. In many metabolic pathways there are mechanisms which control the activity of the pathway. Metabolic flux may be effectively reduced by a regulatory enzyme, but, when a maximum rate is needed, the saturation degree of many of the other enzymes present can be crucial. Moreover, many enzymes are not components of such well controlled pathways. Indeed, metabolism is sensitive to changes in co-factor levels. The severe symptoms of many vitamin deficiencies may be expected to result from a low degree of saturation of one or more of the enzymes which use a deficient co-factor. This suggests that an intermediate degree of saturation may have subtle effects which are important in the long term.

Toxic effects can result from very high levels of some co-factor type nutrients. They are definitely not caused by more perfect saturation of the enzymes for which they serve as co-factors, but by reactions unrelated to their role as co-factors.

THE PHYSIOLOGICAL RELEVANCE OF THE DEGREE OF SATURATION OF ENZYMES

Many nutrients are well known to affect enzyme activities in the body. For example, thiamine, riboflavin and pyridoxine affect enzyme activities in erythrocytes (44-46). Enzyme activity in other tissues also depends on intake levels, but it is not experimentally feasible to determine the degree of saturation of all the relevant enzymes in the human body as a function of intake level.

The effect of intake level on metabolic processes may be illustrated by the case of pyridoxine. A low pyridoxine intake level causes large amounts of tryptophan metabolites to be excreted in the urine in tryptophan loading tests (47). With a normal pyridoxine intake level the same metabolites are processed effectively by the more saturated enzymes and much smaller amounts of metabolites are excreted in the urine. In some people the so-called "Chinese Restaurant Syndrome" results from a large intake of glutamate, which is commonly used as a flavouring in Chinese restaurants. This syndrome may be prevented by increased intake of pyridoxine (48), which apparently saturates an essential enzyme and thus allows a higher metabolic flux when "chemical stress" is induced by glutamate. It is not known which is the most significant enzyme in this case but pyridoxine is a common

co-factor of enzymes in amino acid metabolism. The level of pyridoxine may also affect the steady state concentration of homocysteine, which is a possible factor in arteriosclerosis (49).

Sometimes the saturation level of enzymes may be very relevant to physiological functions. In experiments with laboratory animals many vitamin deficiencies have been found to cause birth defects (50). The same may also be expected in humans. Many vitamin deficiencies, such as scurvy and pellagra, have pronounced psychological symptoms (51, 52). This implies that the functioning of the brain at a psychological level depends on nutrition (6). It has been suggested that nutrient supplementation is beneficial for various medical problems (50, 53-67). Yet the optimal levels of intake with respect to reproduction, mental functions etc. may vary individually so that some people may be affected while most stay healthy with the same level of intake.

The use of large amounts of nutrients in treating psychiatric problems in the orthomolecular approach has been the subject of controversy (68-71). However, it seems that the opposition to the orthomolecular approach is largely based on the nutritional need paradigm, which does not consider the dose-effect relationship of nutrients in brain function to be a relevant consideration in the absence of obvious deficiencies.

CONCLUDING REMARKS

Some objections to the optimal intake approach seem to arise from the wide-spread existence of "quackery" (8, 9, 72, 73). Yet what may be labeled as quackery depends strongly upon which paradigm is used. In a strict nutritional need approach all use of vitamins for a purpose other than dealing with overt deficiency may be called quackery. However, what may appear as blatant quackery in the nutritional need framework may seem a valid claim or a mild exaggeration in the optimum intake framework. Unfortunately, there is much activity in the field of nutrition which may be classified as quackery even from the point of view of the optimum intake paradigm.

In the optimal intake approach there are two basic questions: 1) what are the optimal levels of nutrient intake and 2) how large is the benefit to health caused by optimal intake in comparison with a "normal" or "balanced" diet. There is evidence to suggest that, in many cases, the optimum may be much higher than the RDA level, and that the benefit to health may be large in some cases and noticeable in several others. On the other hand it seems self evident that major chronic diseases, for example, cannot be completely prevented or treated by an optimum diet, even if some alleviation of the illness can be hoped for. Much more experimental work needs to be done to provide more detailed answers to the two questions posed above.

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